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ASETAMİNOFEN VE FENOBARBİTAL KARIŞIMLARININ SUSUZ ORTAMDA TİTRASYONLA TAYİNLERİ

ANALYSIS OF ACETAMINOPHEN AND PHENOBARBITAL COMBINATIONS BY NONAQUEOUS TITRATION

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SUMMARY

The difference in pKa values of aceteminophen and phenobarbital permits differentiation of mixtures containing these drugs. Titrations are performed nonaqueously using tetrabutylammonium hydroxide as the titrant. End–points were determined potentiometrically using a platinium–calomel electrode system. Methylisobutylketon and methylethyl keton were evaluated as solvent for the titration.

ÖZET

Asetaminofen ve fenobarbitalin pKa değerleri arasındaki farklılık, ilaç karışımlarında yanyana bulunan bu iki maddenin ayrılmasına imkan verir. Bu nedenle; bu maddelerin susuz ortamda potansiyometrik yöntemle, Pt–kalomel elektrot sistemi yardımıyla, tetrabutil amonyum hidroksit standart çözelti, metil etil keton ve metil isobutil keton çözücüleri kullanılarak titrasyonları yapıldı.

INTRODUCTION

Acetaminophen and phenobarbital are analgesic and antipyretic compounds often used in combination in tablets, capsules and suppositories. The assay of these active ingredients generally involve time consuming multiple steps; following the separation of the compound different techniques of measurement including HPLC (1–4), TLC (5), spectrophotometry (6), fluorometry (7) and titration (8) were used.

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On the other hand Blake et al. (8) described a nonaqueous titration procedure for a mixture containing acetaminophen and phenobarbital based on the difference in pKa values of these substances. Dimethylformamide was the titration solvent and tetrabutylammonium hydroxide was the titrant. For the analysis each compound a separate aliquot of the sample had to be used in this study.

The present paper, describes a differentiating nonaqueous potentiometric titration procedure for the determination of acetaminophen and phenobarbital combination methylisobuthylketon (MIBK) and methylethyl keton (MEK) were chosen as solvents.

EXPERIMENTAL

Apparatus

Titrations were performed potentiometrically with a titrimeter (Metrohm Harisau Potentiograph, E336A) equipped with a calomel and combined platinum electrode system. The saturated aqueous KCl solution of the calomel electrode was replaced, with a saturated solution of LiCl in methanol. The titrations were made with an automatic burette (Metrohm Harisau, E436) at 25°C stirring the solution with a magnetic stirrer.

Reagents

Phenobarbital, acetaminophen, methylethylketone (MEK) (Merck), methylisobuthylketone (MIBK) (Merck) were obtained from commercial sources. All other chemicals and solvents employed in this study were reagent grade, and they were used without further purification. 0,1 N Tetrabutylammonium hydroxide (TBAH) solution in isopropil alcohol/ methanol (Merck) was standardized against benzoic acid which was restandardized at least weekly during the study.

Differentiating Titration of Synthetic Mixtures

Synthetic mixtures of acetaminophen and phenobarbital were prepared by weighing about (20 – 100 mg) of each component into a 100 ml titration beaker with thermostatic control and dissolving with 25 ml of MEK and MIBK with the aid of a magnetic stirrer at 25°C. The solution was titrated potentiometrically with 0,096 N

tetrabutylammonium hydroxide. During the titration, the tip of the burette was immersed into the titration solution. The end–point in the titration curve was determined from the inflection of the curve obtained by plotting volume of titrant versus millivolt readings.

RESULTS AND DISCUSSION

Differentiating nonaqueous titrimetry has provided a simple and useful technique for determining mixtures of acids or bases. Mixtures of weak acids are analyzable by this technique if the pKa values of the indivudual acids are sufficiently divergent and suitable titrant, titration solvent and electrode are selected.

Acetaminophen and barbiturates are typical weak acids frequently used in analgesic–antipyretic preparations that very often contain other agents. The difference in pKa values of acetaminophen, 9,92 and phenobarbital, 4,47 is sufficiently large to permit a satisfactory differentiating titration (9, 10).

The present study reports the analysis of synthetic mixtures containing acetaminophen and phenobarbital; preliminary extraction of the components was not necessary. Since in dosage forms the amount of acetaminophen is usually considerably higher than that of phenobarbital, the effect of various ratios of these two compounds on the sensitivity of the method was studied. Table 1–2 shows the data for two series of titration in which the milliequivalent weight ratio of phenobarbital to aceteminophen was varied 1.00 : 1.00 to about 1.00 : 0.10.

In the first series MEK, in the second MIBK was used as solvent. Both of them were suitable for this titration. Titrations were effected potentiometrically with 0,096 N TBAH as titrant using a Pt–calomel electrode system and two inflections in the titration curve were obtained as shown in Fig. 1. The first end–point corresponds to phenobarbital and the second end–point is due to acetaminophen. When the ratio was greater than 1.00 : 0.10 only one end–point corresponding to the total acid was realized.

The proposed procedure makes possible the simple, accurate and simultaneous determination of mixtures of acetamihophen and phenobarbital without preliminary extraction of the components.

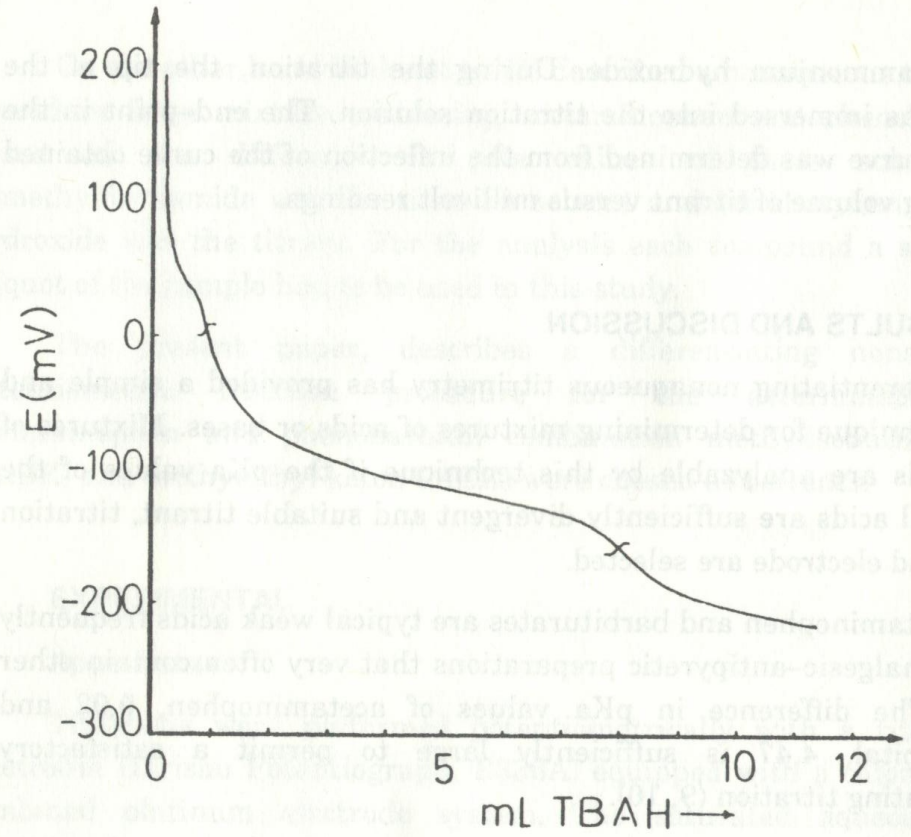

Fig. – 1 : A typical titration curve for a mixture containing acetaminophen and phenobarbital.

Table – I : Analysis of Synthetic Mixtures of Acetaminophen and Phenobarbital by Nonaqueous Titration in Methyl ethyl keton

Meq. Ratio of components		Recovery %	
Acetamino-phen	Pheno-barbital	Acetaminophen	Phenobarbital
1,00 : 1,00		99,81 ± 0,63[a]	99,72 ± 0,57
1,00 : 0,50		100,14 ± 0,55	100,28 ± 0,08
1,00 : 0,33		99,81 ± 0,62	100,32 ± 0,75
1,00 : 0,25		100,13 ± 0,56	98,90 ± 0,48
1,00 : 0,20		99,40 ± 0,44	99,32 ± 0,48
1,00 : 0,15		98,97 ± 0,50	99,86 ± 0,62
1,00 : 0,10		98,93 ± 0,53	99,88 ± 0,49

[a]Average deviation based on at least three determinations.

Table – II : Analysis of Synthetic Mixtures of Acetaminophen and Phenobarbital by Differentiating Nonaqueous Titration in Methyl isobutyl keton

Meq. Ratio of components		Recovery %	
Acetamino-phen	Pheno-barbital	Acetaminophen	Phenobarbital
1,00 :	1,00	96,57 ± 0,42[a]	99,21 ± 0,45
1,00 :	0,50	98,26 ± 0,37	99,74 ± 0,85
1,00 :	0,33	97,93 ± 0,22	101,11 ± 0,87
1,00 :	0,25	100,46 ± 0,63	100,06 ± 0,88
1,00 :	0,20	99,42 ± 0,78	99,98 ± 0,39
1,00 :	0,15	99,18 ± 0,47	101,23 ± 0,49
1,00 :	0,10	97,40 ± 0,32	100,50 ± 0,38

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